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EDITORIAL COMMENT

# Calcium and C-Reactive Protein

## Hot Enough to Predict the Future?*

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> *"My interest is in the future, because I am going to spend the rest of my life there."*
> —Charles F. Kettering (1876–1958), American engineer and inventor of the electric starter (1)

It is very reasonable and most common for a human being to find out about his or her own future. That is why even strict scientists are tempted to make use of fortune tellers and horoscopes. When patients see their physicians, they expect to receive an answer regarding how long they will live and what health problems they may face in the future. This ends frequently in a challenge, because how can one apply statistics to individual recommendations? Answers such as, "You have 10 more years to live" appear unreasonable, even though this may be based on good evidence. Therefore, a good physician will avoid a direct answer and use surrogates to please the patient, such as, "Your laboratory result indicates that you need help." For this answer, 2 things need to be known by the physician: how high the risk is and how the risk can be changed. This applies similarly to primary prevention of coronary artery disease (CAD).

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The classic risk factors for developing CAD are well established and, today, also known by medical laypersons. Individuals with no risk factors such as smoking, diabetes, hypercholesterolemia, or hypertension and no family history of CAD can easily be given good advice, although up to 20% of patients with a coronary event have none of the indicators (2). Similarly, subjects with an overt high-risk profile need no further evaluation, but a clear management. Our energy should be directed toward the intermediate-risk group to better classify them. Here, risk scores, such as the Framingham risk score (FRS), are helpful, but provide only limited incremental information. More may be expected from variables that directly reflect the underlying pathophysiology.

CAD develops very early in life and is usually silent over decades. Its pathomechanism has been extensively studied over the last years, and much interest has been focused on the involvement of calcium. The calcification of the atherosclerotic plaque occurs via an active process resembling bone formation and is controlled by complex enzymatic and cellular pathways (3). Recently, numerous studies were able to show the attendance of osteoblast-like cells, transcription factors, and bone morphogenetic proteins in the process of calcification. The initiating mechanism of calcification requires apoptosis of smooth muscle cells to generate apoptotic bodies that act as nucleating foci of calcification, inflammation, lipoprotein and phospholipid accumulation, and finally, hydroxyapatite deposition. The dignity of calcification has been investigated extensively. However, whether it is a benign bystander or a truly suspicious finding is so far unknown. Nevertheless, there is good evidence that mainly spotty calcification is a feature of vulnerability and is closely related to plaque rupture, eventually resulting in life-threatening events. Increasing prevalence of CAD translates into very large costs to society, which could be attenuated if better models of prediction of atherosclerosis are available. Accordingly, many indirect approaches such as the carotid intima-media thickness and various markers of peripheral arterial stiffness have been proposed. However, the direct assessment of coronary plaque burden and the activity of the process appear more attractive. The tools to achieve this information are currently best provided by a combination of imaging modalities and biomarkers.

### Biomarkers and Prognosis

A great number of biomarkers have been investigated over recent years, reflecting different pathophysiologic mechanisms in acute coronary syndromes and in stable angina. Less well investigated is the role of biomarkers in primary prevention settings.

The most promising appear to be markers that indicate the transition of a silent to a vulnerable plaque. Accordingly, most of the investigated markers reflect inflammation, such as interleukins, myeloperoxidase, neopterin, matrix metalloproteinase (MMP)-9, and monocyte attracting protein (MCP)-1. Best established is high-sensitivity C-reactive protein (hsCRP), which is an acute-phase reactant and therefore rather unspecific for local processes (4). However, hsCRP can serve as a target for therapy, which is of paramount importance in translating results to clinical practice (5).

Many other novel biomarkers reflecting elegantly local plaque activity and vulnerability, such as growth differentiation factor (GDF)-15 or lipoprotein-associated phospho-

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lipase A2 (Lp-PLA2), provide independent prognostic information in patients with acute coronary syndromes and stable CAD, but may be less predictive in primary prevention with follow-up over many years (6).

Another approach is to measure markers of myocardial function, like the B-type natriuretic peptide (BNP) and the biologically inactive split product N-terminal (NT)-proBNP, which are already routinely available to evaluate patients with dyspnea. Both were shown to be good predictors in patients with acute coronary syndromes and stable CAD (7). Recently, a strong association between BNP and the severity of coronary atherosclerosis has been demonstrated. However, BNP does not primarily reflect coronary plaque burden but may rather indicate myocardial ischemia even if clinically silent (8,9). Furthermore, so far, no therapeutic strategy could be identified to influence the adverse prognosis associated with elevated BNP levels.

## Imaging of Plaque Burden

Different strategies have been developed to assess plaque burden including invasive and noninvasive tools (electron-beam computed tomography [EBCT], computed tomography [CT], magnetic resonance imaging, and positron emission tomography/CT). The Agatston score as measure of overall coronary artery calcification (CAC), introduced by EBCT, has been further developed in the setting of multislice CT, which has the additional benefit of coronary angiography with the possibility to image single plaques and their different compositions. This can be achieved by only moderate exposure to ionizing radiation, which is generally in the range of 0.5 to 1.0 mSV, and is therefore rather negligible.

It could be shown that CAC in addition to the classic risk factors increases the predictive power for coronary events (10). However, there remain major concerns related to the role of calcifications in atherosclerosis, which is still not completely elucidated. Calcifications grow as atherosclerosis progresses as a function of aging and may develop toward stenotic lesions. However, it remains unclear whether calcification stabilizes atheromas or makes them more prone to rupture. In a comparison of acute and chronic events, acute events were found to have considerably lower CAC scores compared with chronic events (63 vs. 906) (11). In contrast, other evidence shows that spotty calcification and presence at the shoulders of plaques increase the risk of rupture (12). This dilemma is nicely reflected in a recent study demonstrating that lesions of acute coronary syndromes have less absolute calcium content but more frequently a spotty calcification pattern (13). Accordingly, a person with little or even no calcium is not entirely safe from coronary events.

## Combination of Biomarkers and Imaging

Risk assessment of CAD with both biomarkers and different imaging modalities has distinct shortcomings. However, combining both approaches may overcome the methods' individual limitations. In this issue of the *Journal*, Möhlenkamp et al. (14) demonstrated that such a combination of hsCRP and CAC (by EBCT) is able to identify patients at very high risk for coronary events. A total of 3,966 subjects of the well-defined, prospective Heinz Nixdorf Recall study, with known hsCRP and CAC, were included and followed up for over 5 years (mean 5.1 ± 0.3 years). Both predictors independently and accurately identified coronary events and all-cause mortality. Furthermore, net reclassification as a measure of incremental prognostic information improved the prediction of coronary events by 10.5% for hsCRP and 23.8% for CAC, respectively.

When introducing a new diagnostic test or a combination of such, one expects an improved prediction of events. The ability of a test to make such a prediction is called *discrimination*. When more than 2 categories of increasing risk are used, we expect the test to have the same prognostic value across all categories, an ability called *calibration*.

There is an ongoing debate about which statistical test most accurately reflects incremental diagnostic value. The traditional c-statistic has recently been criticized because of its limited power to detect and reflect improved prediction. The net reclassification index as a measure of how many patients are reclassified into a category that better suits their outcome and the integrated discrimination index as a continuous measure of prediction are currently considered the gold standard of testing risk measure (15). Here, the authors show improved diagnostic performance with all aforementioned tests, a thoroughness that underlines the benefit of their risk score.

The authors also show that their newly introduced score is well calibrated. This is especially interesting as they outperform the classic FRS in all risk categories and reclassify patients in all of the 3 FRS categories in all possible directions.

## Practical Considerations

What practical conclusions arise from these findings? Patients who are considered to be at high risk for cardiovascular events given an increased level of hsCRP, but otherwise apparently healthy, have been treated in the JUPITER (Justification for the Use of statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial with rosuvastatin as primary prophylaxis (5). This intervention could reduce cardiovascular events by one-half over a period of 2 years, suggesting that risk stratification and decision making according to elevated hsCRP levels can indeed change the individual's future significantly. However, these results have to be challenged in 2 ways: First, we still don't know whether the intervention, that is, aggressive lipid lowering in the absence of overt disease, improves the outcome independently from elevated hsCRP. Second, a large-scale genome-wide association-based study found no concordance between the effect on CAD risk of CRP genotypes

and CRP levels, which strongly argues against a causal association of CRP with CAD (16).

Likewise, it is unclear what practical implications emerge from high CAC scores since it is to date not known which role CAC might play in predicting the vulnerability of single plaques and, therefore, the immediate, not stochastic, risk of a single patient.

Furthermore, socioeconomic aspects have to be considered against the background of limited health care resources. Given the relatively low event rate reported in the Nixdorf Recall Study and the likewise low percentage of patients reclassified into the high-risk group due to hsCRP or CAC findings, it has to be assumed that the "number needed to reclassify," that is, the number of patients that has to undergo hsCRP measurement and a CT for CAC to predict 1 cardiovascular event, is rather high, and even then we still have no definite concept as to how to avoid this event. This assumption is further supported by the fact that more patients died from cancer than from cardiovascular causes.

Getting back to the future: applying the methods proposed by Möhlenkamp et al. (14) definitely makes us better medical fortune tellers, but how to translate this knowledge into a better treatment in order to become better doctors has yet to be defined.

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## REFERENCES

1. Brainy Quotes. Charles Kettering Quotes. Available at: http://www.brainyquote.com/quotes/authors/c/charles_kettering.html. Accessed February 17, 2011.
2. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003;290:898–904.
3. Johnson RC, Leopold JA, Loscalzo J. Vascular calcification: pathobiological mechanisms and clinical implications. Circ Res 2006;99:1044–59.
4. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557–65.
5. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
6. Schnabel RB, Schulz A, Messow CM, et al. Multiple marker approach to risk stratification in patients with stable coronary artery disease. Eur Heart J 2010;31:3024–31.
7. Blankenberg S, McQueen MJ, Smieja M, et al. Comparative impact of multiple biomarkers and N-terminal pro-brain natriuretic peptide in the context of conventional risk factors for the prediction of recurrent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study. Circulation 2006;114:201–8.
8. Mollmann H, Nef HM, Kostin S, et al. Ischemia triggers BNP expression in the human myocardium independent from mechanical stress. Int J Cardiol 143:289–97.
9. Weber M, Bazzino O, Navarro Estrada JL, et al. N-terminal B-type natriuretic peptide assessment provides incremental prognostic information in patients with acute coronary syndromes and normal troponin T values upon admission. J Am Coll Cardiol 2008;51:1188–95.
10. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–45.
11. Shemesh J, Apter S, Itzchak Y, Motro M. Coronary calcification compared in patients with acute versus in those with chronic coronary events by using dual-sector spiral CT. Radiology 2003;226:483–8.
12. Ehara S, Kobayashi Y, Yoshiyama M, et al. Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. Circulation 2004;110:3424–9.
13. Pflederer T, Marwan M, Schepis T, et al. Characterization of culprit lesions in acute coronary syndromes using coronary dual-source CT angiography. Atherosclerosis 2010;211:437–44.
14. Möhlenkamp S, Lehmann N, Moebus S, et al., on behalf of the Heinz Nixdorf Recall Study Investigators. Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality. J Am Coll Cardiol 2011;57:1455–64.
15. Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. Clin Chem 2008;54:17–23.
16. Elliott P, Chambers JC, Zhang W, et al. Genetic loci associated with C-reactive protein levels and risk of coronary heart disease. JAMA 2009;302:37–48.

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